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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/673,735	12/27/2000	Bernd Dorken	028622/0102	3749

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EXAMINER	
HELMS, LARRY RONALD	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/673,735	DORKEN ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,20-23,30,33 and 35-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12/27/00*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election with traverse of Group I claims 1-16, 21-23 in part and newly submitted claims 35 and 36 in Paper filed 10/24/03 is acknowledged. The traversal is on the ground(s) that the antibody of Jonge et al does not bind human CD3. This is found persuasive and as such claims 1-16, 20-23, 30, 33, 35-43 will be examined together. The claims are directed to three groups, product, process of use and process of making. Applicants are reminded that any other claims submitted to inventions distinct from those currently examined will be restricted under 37 CFR 1.475 and 1.499.

2. Claims 17-19, 24-29, 31, 32, 34 have been canceled and claims 35-43 have been added.

3. Claims 1-16, 20-23, 30, 33, 35-43 are pending and under examination.

Specification

4. The disclosure is objected to because of the following informalities:

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see page 27 for example). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-4, 21-23, 30, 33, 35-38, 40-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1, 21, 30 and those depending from these claims are indefinite for reciting 'a first domain comprising a binding-site of an immunoglobulin chain or an antibody" because is the domain from a binding site of an immunoglobulin or is the domain an antibody or is the domain an antigen binding region of an antibody?

B. Claims 1, 21, 30 and those depending from these claims are indefinite for reciting "a single-chain multifunctional polypeptide...an antibody specifically recognizing the Cd19 antigen; and ...an antibody specifically recognizing the human CD3 antigen" because it is unclear how a single-chain polypeptide can be an antibody or made up from an antibody because antibodies are made up of multiple chains of polypeptides not just one chain.

C. Claims 3, 37 and 41 and those claims dependent from these claims are indefinite for reciting "mimic" a VH and VL region because the exact meaning of the term ins not clear. How does the polypeptide "mimic" the VH or VL region? Does it have the same binding specificity, sequence or altered sequence, etc?

D. Claim 4 recites the limitation "said antibody" in claim3. There is insufficient antecedent basis for this limitation in the claim.

E. Claim 40 is indefinite for reciting "The method of claim 20, comprising at least one further domain" because claim 20 is a method of preparing a single chain antibody of claim one which only has two domains.

7. Claim 11 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a single chain multifunctional polypeptide that binds CD19 and human CD3 wherein the binding domain of CD3 comprises six CDRs encoded by nucleotides 847 to 1203 and 1258 to 1575 of SEQ ID NO:9 or any other nucleotide that encodes six CDRs from a binding site of an antibody that binds CD3 and the CD19 binding site comprises six CDRs and is encoded by a nucleic acid of 82 to 414 and 460 to 831 of SEQ ID NO:9 or a nucleic acid encoding a binding site of an antibody that binds CD19, does not reasonably provide enablement for any single chain polypeptide that binds CD3 and CD19 which does not comprise an entire binding site of an antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the

breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to single chain multi functional polypeptide that binds CD3 and CD19 which does not comprise all six CDRs from the heavy and light chain of the antibody or CDRs from one antibody and CDRs from another antibody.

The specification teaches an single chain bispecific antibody that binds human CD3 and CD19 that comprises six CDRs and the specification teaches that six CDRs confer antigen binding (see page 8).

The claims are not commensurate in scope with the enablement provided in the specification.

It is well established in the art, and stated in the specification on page 8, that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid

sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that polypeptidesas defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an antibody have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-16, 20-23, 30, 33, 35-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bohlen et al (Blood 82:1803-1812, 1993), and further in view of Mack et al (PNAS 92:7021-7025, 1995) and as evidenced from the specification and Blattler et al (US Patent 5,239,062, filed 7/90).

The claims recite a bispecific single chain antibody that binds CD19 and human CD3 wherein the domains are arranged as VLCD19-VHCD19-VHCD3-VLCD3 and the linker comprises 1- 5 amino acids or a plurality or consecutive copies and comprises glycine, ala, serine or combinations thereof and GLY GLY GLY GLY SER and the

polypeptide comprises at least one CDR encoded by 847-1203 and 1258 to 1575 of SEQ ID NO:9 and the polypeptide has affinity of at least 10-7 M and the polypeptide has a domain capable of sequestering an ion and a method of preparing such and compositions comprising such and methods of treatment of non-Hodgkins lymphoma with such antibody.

Bohlen et al teach a bispecific antibody that binds CD19 and human CD3 and a method of preparing such and a method to treat B-chronic lymphocytic leukemia (B-CLL) with the bispecific antibody. Bohlen et al does not teach a single chain bispecific CD19 X human CD3 antibody or methods to treat non-Hodgkin's lymphoma with an antibody. These deficiencies are made up for in the teachings of Mack et and Blattler et al.

Mack et al teach a single chain bispecific antibody that binds human CD3 and 17-1 and the domains are linked with a GLY4SER or (GLY4SER)4 and the domains are linked VL-VH-VH-VL and the CD3 binding domain comprises the CDRs encoded by nucleotides 847-1203 and 1258-1575 of SEQ ID NO:9 (as evidenced from the specification on page 33-34 the CD3 binding site was from Mack (PNAS 92:7021-5, 1995)) and the single chain molecule has a third domain of a histidine tail and FLAG tag (see Figure 1) and methods of treating cancer and methods of producing such single chain antibody. Mack also teach obtaining the variable domains of an antibody by PCR (see page 7020). Mack et al also teach the disadvantages of making bispecific antibodies by hybridoma technology and the advantages of producing single chain antibodies and there ease of purification and that the small size of the single chains may

be more efficacious than intact antibodies (see abstract) and the single chain antibodies were highly cytotoxic for tumor cells at nanomolar concentrations (see page 7021).

Blattler et al teach the CD19 antigen is expressed in all B-CLL and in all non Hodgkin's lymphomas (see column 6, lines 46-55).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a single chain bispecific antibody from the bispecific antibody of Bohlen et al by the method of Mack et al for the treatment of non-Hodgkin's lymphoma.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a single chain bispecific antibody from the bispecific antibody of Bohlen et al by the method of Mack et al for the treatment of non-Hodgkin's lymphoma because Bohlen et al teach that a bispecific binding agent which binds CD19 and human CD3 can be used for the treatment of B-CLL and as taught by Blattler et al the CD19 antigen is expressed in all B cell non-Hodgkin's lymphomas. Therefore it would have been obvious to treat Non-Hodgkin's lymphoma with a bispecific molecule, specifically a bispecific single chain antibody directed to CD19 and CD3. In addition, One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a single chain bispecific antibody from the bispecific antibody of Bohlen et al by the method of Mack et al for the treatment of non-Hodgkin's lymphoma because Mack et al teach the advantages of using single chain bispecific antibodies because of their ease in purification and it would have been obvious to obtain the cDNA sequence of the

hybidoma of Bohlen for the CD19 binding site because Mack teach standard PCR methods were used to obtain the variable regions from the hybridomas. Therefore, it would have been obvious to make a single chain bispecific antibody that binds CD19 and human CD3 from the antibody of Bohlen because of the advantages of single chain antibodies as taught by Mack and it would have been obvious for the treatment of non-Hodgkin's lymphoma because Bohlen teach the bispecific molecule can treat B-CLL which express CD19 and as taught by Blattler that all B cell non-Hodgkin's lymphomas express CD19.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of

this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

LARRY R. HELMS, PH.D
PRIMARY EXAMINER